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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09 529,722	04 19 2000	DAVID J SQUIRRELL	124-765	3335

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EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07 02 2002

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/529,722

Applicant(s)

SQUIRRELL ET AL.

Examiner

David J. Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 April 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

Application Status

Claims 33-46 are pending in the application.

Applicants' amendment to the specification, cancellation of claims 19-32, and addition of claims 33-46 in Paper No. 18, filed 04/24/02, is acknowledged.

Applicants' arguments filed in Paper No. 18 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Oath/Declaration

1. The oath or declaration remains objected to as being defective. It is noted that applicants will file a new oath or declaration in compliance with 37 CFR 1.67(a) as requested in a previous Office action. As a new oath or declaration has not yet been filed, the oath or declaration is objected to for the reasons of record.

Drawings

2. Applicants' request for review of the submitted drawings is acknowledged. In a previous Office action, the examiner stated the drawings submitted with this application had not been reviewed by a draftsman. This was an oversight by the examiner as it appears that no drawings were submitted with the instant application.

Claim Objections

3. Claim 34 is objected to in the recitation of "cultures" in line 1. It appears the term should be replaced with "cultured" and the claim has been examined accordingly.

Claim Rejections - 35 USC § 112, Second Paragraph

4. Claims 33-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 33 (claims 34, 37, and 46 dependent therefrom), 35, 36, 38 (claims 39-41 dependent therefrom), 42, and 43 (claims 44 and 45 dependent therefrom) are indefinite in the recitation of "luciferase remains unaffected" (claims 33, 35, and 36), "luciferase is not adversely affected" (claim 38), and "luciferase protein is not adversely affected" (claim 42). It is unclear from the claims and the specification as to what structural or functional characteristic of a luciferase remains "unaffected". It is suggested that applicants clarify the meaning of the term.

6. Claim 42 is indefinite in the recitation of "a luciferase which retains a luciferase activity". It is unclear from the claims and the specification as to the retained luciferase activity. It is suggested that applicants clearly identify the retained activity.

Claim Rejections - 35 USC § 112, First Paragraph

7. The written description rejection of claims 33-36 and 37-46 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

It is noted that applicants have not addressed the written description and scope of enablement rejections individually and the examiner has made an earnest attempt to fully address applicants' response to the rejections. Applicants argue the recitation of a particular luciferase (Luc) or adenylate kinase (AK) should not be required as the disclosed method is not dependent on or does not require any specific thermostable Luc and/or E. coli AK with mutations at amino acid 87 or 107 as the claimed method is useful with any AK. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

It is noted that claims 38-41 are not drawn to methods and are instead drawn to a recombinant cell comprising nucleic acid sequences encoding a thermostable Luc and a mutant AK that is denatured

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under pH or temperature conditions of 37 °C or more. The specification teaches the structure of only one representative species of mutant AK polypeptides, namely, *E. coli* AK with mutations at positions 87 or 107 that is inactivated at temperatures of 40 °C or greater. As previously stated, genes encoding mutant AK polypeptides as recited in the claims *were not* well known in the art at the time of the invention. The genus of genes encoding mutant AK polypeptides recited in the claims, i.e., a gene encoding a mutant AK that is denatured under pH or temperature conditions of 37 °C or more is an insufficient description of the claimed genus of encoding genes as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". While it is acknowledged that claims 33-37 and 42-46 are drawn to *methods* for producing thermostable Luc free of AK, the functional definition of the recited genus of genes encoding mutant AK polypeptides does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus. Therefore, the specification fails to sufficiently describe the claimed invention, in such full, clear, concise and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

8. The scope of enablement rejection of claims 33-36 and 37-46 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Regarding the temperature and pH conditions, applicants argue it is clear that the required temperature for denaturation of the AK polypeptide is 37 °C or more and that it requires routine

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experimentation to identify an upper temperature at which a Luc becomes unstable. Applicants argue that similarly with pH conditions, it would require routine experimentation for a skilled artisan to generate an AK that would be unstable under certain pH conditions. Applicants argue the examiner's position appears to be that the claims encompass any Luc that is stable under any pH or temperature conditions and any AK that is unstable under any pH or temperature conditions. Applicants argue the claims cover a method for producing Luc free of AK under pH or temperature conditions that denature AK while Luc retains enzymatic activity. Applicants argue the claims are limited to conditions at which the AK is denatured while Luc maintains enzymatic activity. Applicants argue they should be rewarded with the entire scope of the claimed invention. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

As noted above, claims 38-41 are not drawn to methods and are instead drawn to a recombinant cell comprising nucleic acid sequences encoding a thermostable Luc and a mutant AK that is denatured under pH or temperature conditions of 37 °C or more. The specification is enabling for a recombinant cell comprising a polynucleotide encoding a Luc that is thermostable at temperatures of 37 °C or more and a polynucleotide encoding a mutant AK polypeptide that is inactivated at temperatures of 37 °C or more, wherein the Luc maintains at least partial enzymatic activity and methods of making said recombinant cell or using said recombinant cell for the production of Luc. The scope of the claims is broader than the enablement provided by the specification. The specification does not provide guidance as to nucleic acids encoding Luc polypeptides that retain enzymatic activity under particular conditions and nucleic acids that encode AK polypeptides that are inactivated at the same conditions and no guidance or working example has been disclosed to obtain a recombinant cell comprising said nucleic acids or methods of making or use thereof. The specification only provides guidance and a working example to demonstrate a recombinant cell comprising a nucleic acid encoding a Luc that is stable at 37 °C or more and a nucleic acid encoding E. coli AK that is denatured at 37 °C or more. At the time of the invention, genes encoding AK polypeptides that are inactivated at 37 °C or more were not well known in the art. Also, at the time of the invention, nucleic acids encoding Luc polypeptides stable at a particular pH and nucleic acids

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encoding an AK polypeptide that is inactivated at the same pH were not well known in the art and no guidance or working example has been disclosed to obtain a recombinant cell comprising said nucleic acids or methods of making or use thereof. Methods of generating such nucleic acids are highly unpredictable and the generation of such nucleic acids would require undue experimentation. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

9. The rejection of claims 33-46 under 35 U.S.C. 103(a) as being unpatentable over EP 373962 in view of Belinga et al. (J Chromat A 695:33-40), Gilles (Proc Natl Acad Sci, USA 83:5798-5802), and Kajiyama et al. (Biochemistry 32:13795-13799) is maintained. The rejection was fully explained in a previous Office action.

Applicants argue the examiner has impermissibly used hindsight and applicants state they are surprised in view of paragraph 10 of Paper No. 4. Regarding the reference of EP 373962 (also referred to as Backman in Paper No. 18), applicants argue that the claimed invention would not have been obvious to an ordinarily skilled artisan based on the teachings of EP 373962 as the contaminants that are removed are not mutant contaminant proteins, particularly mutant AK. Regarding the reference of Belinga, applicants argue that the claimed invention would not have been obvious to an ordinarily skilled artisan as Belinga does not teach all limitations of the claimed invention or teach or suggest removal of a specific contaminant. Applicants argue there is no motivation in the prior art to improve on the method of purifying Luc as taught by Belinga. Regarding the reference of US Patent 5,229,285, applicants argue that the claimed invention would not have been obvious to an ordinarily skilled artisan as US Patent 5,229,285 does not teach the removal of a contaminant protein when purifying the luciferase. Regarding the reference of Gilles, applicants argue that the claimed invention would not have been obvious to an ordinarily skilled artisan based on the teachings of Gilles, as no teachings or suggestion is presented in Gilles to make obvious the claimed invention. Applicants argue Gilles is a relatively old document and yet

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no one has yet to invent the claimed recombinant cell or methods. Applicants allege the mutant AK of Gilles is not temperature sensitive and actually has increased activity at 43 °C. Applicants argue the deficiencies of EP 373962 are not overcome by Belinga, US Patent 5,229,285, or Gilles and the combination of references of EP 373962, Belinga, US Patent 5,229,285, and Gilles do not teach all limitations of the claimed invention or provide a motivation for making or practicing the claimed invention and therefore the invention of the claims is not rendered obvious to one of ordinary skill in the art. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

It is noted that in order for the examiner to consider experimental evidence, applicants should submit such evidence in the form of a declaration under 37 CFR 1.132. As such, the examiner has not considered applicants data regarding the AK of Gilles. Applicants are advised that such a submission may affect the enablement of the claimed invention provided by the instant specification (see page 7, lines 28 and 29 of the instant specification), particularly to claim 37 and 46. Also, in response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. While each of the references alone or a subcombination thereof does not teach all limitations of the claimed invention, provide motivation or provide a reasonable expectation of success for making or practicing the claimed invention, the combination of all cited references renders the claimed invention *prima facie* obvious. While the reference of EP 373962 does not specifically teach purification of a thermostable protein from a *mutant* thermolabile contaminant, EP 373962 clearly suggests engineering a host cell to produce a thermostable protein from *any* unwanted contaminant, e.g., a mutant thermolabile protein, without restricting the type of contaminating protein to be removed. One of skill in the art would have been motivated to purify thermostable Luc from thermosensitive AK using the method as taught by EP 373962 as column chromatography is time consuming and costly relative to purification by heat denaturation as taught by EP 373962. To make the claimed recombinant cell, one of ordinary skill in the art must only transform the host cell of Gilles with an expression vector encoding a thermostable Luc and to use said recombinant cell for purification of thermostable Luc from thermosensitive AK, an ordinarily skilled artisan must only use

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the cell to practice the method of EP 373962. The combination of the cited references teaches the claim limitations, provides motivation and a reasonable expectation of success for practicing the claimed invention. The rejection is maintained for the reasons of record and the reasons presented above.

Conclusion

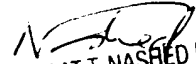
10. No claim is in condition for allowance. All claims are rejected.

Applicants' amendment to claims 33, 35, 36, 38, 42, and 43 necessitated the new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.


NASHAAT T. NASHED PHD.
PRIMARY EXAMINER